Webinar: CIRM human induced pluripotent stem cell (hiPSC) Initiative

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CIRM conducted a webinar on July 19, 2012 to provide information regarding RFAs 12-02, 12-03 and 12-04 including an overview of the application process and questions from applicants. Archived materials from this webinar are available below for your reference.

Webinar Resources

Slides

- Download the slide presentation from the webinar [pdf]

Webinar Recording

- Listen to the webinar with slides

FAQs

Questions relevant to RFA 12-02

1. Do fibroblasts have to be the source tissue? Could blood cells be the source tissue for generation of hiPSC? / Regarding RFA 12-02, will an applicant be evaluated on what type of tissue they can provide? For example, if only blood can be provided, would that be a concern? / Is there a specific type of tissue preferred for collection (i.e. skin vs. surgical resection samples, etc.)
2. For RFA 12-02, can the procurement of patient samples come from outside of California (or do the samples need to come from within California)?
3. For RFA 12-02, is there a preference for individual clinic contributors (i.e., disease-oriented) vs. a more diverse contributor (i.e., an entire department of medicine)?
4. Will the GWG suggest changes? I can easily find 3000 AD patients for a collection, but I doubt if the GWG will like that – in spite of the fact that chances of finding a phenotype are great with 3000? / Might only a subset of patient samples be selected from an RFA 12-02 application and the budget be adjusted accordingly?
5. Can tissues collected from a range of individuals be over a broad range of ages (children vs. adults vs. geriatric)?
6. Will characterization of physiological functionality of the originating disease tissue be considered a useful addition to the medical information?
7. GWA studies suggest that tens of thousands of individuals are necessary for the identification of polygenic effects. Should we be choosing individuals who have shown positive correlations in published GWA studies? If so, can we access these patients?
8. RFA 12-02 suggests funding 3 to 10 grants and lists 14 diseases. Does CIRM have a specific number in mind for the number of tissue donors for each disease? A minimum? A maximum? / Do you have a preferred range of sample sizes per disease?
9. Is there a concern about using EBV-transformed lymphoblastoid cell collections? Will we need to show genomic integrity before hiPSC derivation?
10. For RFA 12-02, are tissues from autopsy patients eligible for consideration?
11. Is there a specific timeframe for the tissue collection?

Questions relevant to RFA 12-03

12. You have mentioned in RFA 12-03 that to be eligible for this award, the applicant organization must have secured a location in California at the time of submission of an application. Does this mean we need to have a physical location in California when we apply, or can we wait until we are awarded?
13. According to RFA 12-03, CIRM intends to commit up to $16 million total to support one (1) hiPSC derivation project for up to three (3) years for deriving three hiPSC lines from each of 3000 or more tissue samples (includes control samples). Our calculations suggest that a total of $16 million for the derivation and characterization of 9000 quality lines is incompatible with current costs. Please comment.
14. How many vials per hiPSC lines should the Deriver provide to the Repository? How many cells per vial? At what stage (passage

after picking) of hiPSC generation do you want the cells to be cryopreserved?

15. Regarding characterization of hiPSC lines, what are the minimum release criteria to approve the quality of derived hiPSCs? As per RFA12-03, "The Deriver and the Repository shall agree on the full scope of hiPSC line testing required before the transfer of lines to the Repository." Characterization is one of the main cost drivers and would be important to know before we submit a proposal.
16. What quality control measures do you really want? Is genomic stability important, or do you expect something like an Oct4 stain only?
17. People are mosaic and cultures are heterogeneous. Will there be criteria to determine whether the iPSC represent the patient?
18. Who will be responsible for the quality of the derived hiPSC lines, in particular karyotype, the Deriver or Repository?
19. Will the Genomics Center have any interaction with the hiPSC generation effort – for QC, for example? / Are some of the hiPSC characterization costs going to be covered by the Genomics RFAs and if so, when will we hear about the details of the Genomics RFA?
20. What percentage of primary cells will not be skin or blood derived?
21. If a skin biopsy is collected, who is responsible for generating the fibroblasts?
22. Does DNA rearrangement in blood cells matter?

Questions relevant to RFA 12-04

23. For the CIRM hPSC Repository Award, if an organization has facilities in both California and in another state, can the hiPSC lines be prepared and cryopreserved in the other state and stored and distributed from California?
24. Who will be responsible for the quality of the derived hiPSC lines, in particular karyotype, the Deriver or Repository?
25. Will the primary source cell lines be redistributed to any investigator who requests them?
26. Will the 2 hiPSC lines per tissue donor stored as a reserve be distributed, as they may not have exactly the same differentiation potential as the clone used for primary distribution?
27. How many additional cell lines, generated outside this hiPSC Initiative, are expected to be banked?

General Questions relevant to the hiPSC Initiative

28. How will the reviewers balance a 12-03 application that plans to provide for example, 2 vials per line and a banking application that requires, for example, 6-10 vials to start the bank? Will there be a chance to coordinate these activities to minimize costs?
29. Is there a limit to the number of pages of supporting documents that can be submitted under Part D, such as dozens of pages of Protocols and SOPs? Also, can we submit scientific data under Part D?
30. RFA 12-02 describes both facilities and indirect costs. What is the difference? And, are such costs part of, or in addition to, the $4 million total costs set aside for these awards? (Although directed at RFA 12-02, this question and answer applies to all 3 hiPSC Initiative RFAs)
31. Just to be clear, the $16 million for the Deriver includes institutional indirect cost? (Although directed at RFA 12-03, this question and answer applies to all 3 hiPSC Initiative RFAs, each with a different $ amount)
32. Who is responsible for pathogen testing (e.g. HIV, HBV, etc.) of the primary tissue sample? The collector or the deriver?
33. Will all MTAs need to go through an approval loop through CIRM?
34. Can an individual apply to more than one RFA?
35. For RFA 12-02/12-03, if more than 3000 samples are contributed, what are the criteria for the tissue expansion and iPS cell derivation?
36. Are there more details for the shipping and distribution of the material?
37. Will the CIRM hiPSC Initiative only fund big centers? Is it a waste of time for innovative young investigators to apply for this opportunity?
38. Why does RFA 12-02 target polygenic diseases?
39. Because of the focus on polygenic diseases in RFA 12-02, there are no hESC lines that represent these diseases. Will there be a separate opportunity for hESC collections?
40. Will the same group of reviewers be reviewing 12-03 and 12-04 (hiPSC generation and banking)?
41. Drug toxicity is the 4th leading cause of death in the US. Ethnically or genomically diverse iPSCs could be used to test drugs for toxicity early in the pipeline. Does CIRM have an interest in using iPSC for toxicity testing during drug development?
42. Will there be opportunities for interaction with the grantees by researchers who regularly make their own iPSCs? A lot of researchers have valuable tissue collections already established. Will they be able to make use of the infrastructure?

Questions relevant to RFA 12-02

1. Do fibroblasts have to be the source tissue? Could blood cells be the source tissue for generation of hiPSC? / Regarding RFA 12-02, will an applicant be evaluated on what type of tissue they can provide? For example, if only blood can be provided, would that be a concern? / Is there a specific type of tissue preferred for collection (i.e. skin vs. surgical resection samples, etc.)

In order to enable the procurement of uniform starting material, RFA 12-03 applicants (derivation) will propose the tissue type they prefer to use for hiPSC derivation. The goal is that the majority of Tissue Collectors will collect the tissue type requested by the Deriver; this is likely to be blood or skin. If the Deriver prefers skin, but a Tissue Collector prefers blood, such discrepancies will be the basis for negotiations once funding decisions have been made. If the Tissue Collector can only provide blood, they should state that in their application, but this will not be evaluated by the reviewers.
If RFA 12-02 applicants make the case that neither blood nor skin can or should be collected from the targeted patient population, then we ask them to justify that choice (see section IX.B.11, page 16), which will be evaluated by the reviewers. In that case and once funding decisions have been made, the Tissue Collector would work with the Deriver to ensure that the alternate tissue can be appropriately shipped and used for hiPSC derivation.

2. For RFA 12-02, can the procurement of patient samples come from outside of California (or do the samples need to come from within California)?

CIRM recognizes that some patient cohorts with particularly study-worthy genotypes or phenotypes exist outside of California. In order to enable their inclusion, RFA 12-02 states in section IX.B.5, under Consultants/Subcontracts (page 14), that increases to CIRM's limits on funding out-of-state activities may be allowed with appropriate justification.

3. For RFA 12-02, is there a preference for individual clinic contributors (i.e., disease-oriented) vs. a more diverse contributor (i.e., an entire department of medicine)?

The individual applications to RFA 12-02 each have to have a specific disease focus, with well-argued rationale for inclusion in the CIRM hiPSC Initiative. The Principal Investigator, though, can choose to work with multiple co-investigators / collaborators to achieve the desired recruitment of tissue donors for the chosen disease. If a department of medicine has access to potential tissue donors representing several diseases that warrant inclusion in the hiPSC Initiative, an option would be for different individuals from that department to each serve as a PI on a separate application for each given disease.

4. Will the GWG suggest changes? I can easily find 3000 AD patients for a collection, but I doubt if the GWG will like that – in spite of the fact that chances of finding a phenotype are great with 3000? / Might only a subset of patient samples be selected from an RFA 12-02 application and the budget be adjusted accordingly?

In principle yes, although the Grants Working Group does not routinely modify proposals. In your application, you will have to justify the number of tissue donors you propose to include and you will have to demonstrate your ability to recruit those tissue donors and to collect the tissues and the proposed associated demographic, medical and diagnostic information.

However, in rare circumstances it is possible that the Grants Working Group review panel will find that hiPSC-based modeling for a given disease could be achieved with fewer tissue donors than proposed, in which case they could recommend to CIRM's governing board, who will make final funding decisions, that the proposed number of tissue donors, and correspondingly the budget, be reduced.

5. Can tissues collected from a range of individuals be over a broad range of ages (children vs. adults vs. geriatric)?

Yes. It is the responsibility of the applicants to RFA 12-02 to justify the age distribution they propose for sample collection, and the reviewers will address that rationale in the context of the targeted disease.

6. Will characterization of physiological functionality of the originating disease tissue be considered a useful addition to the medical information?

In most cases, the tissue collected for hiPSC derivation will not be the tissue affected in the targeted disease. However, should that be the case, knowledge of the physiological functionality of the tissue whose cells were used for hiPSC derivation may be useful should issues arise when hiPSC lines are used by the end-user. More generally, such information may add to the phenotypic characterization of the patient; it will be the responsibility of RFA 12-02 applicants to describe how the collected medical information will facilitate discovery of disease-related phenotypes in hiPSC-based disease models (RFA 12-02, section IX.B.12).

7. GWA studies suggest that tens of thousands of individuals are necessary for the identification of polygenic effects. Should we be choosing individuals who have shown positive correlations in published GWA studies? If so, can we access these patients?

The answer to the first question is "Yes", except the results from GWA studies would not have to published (although peer review would improve the validity of such a study). Tissue donors with genetically complex diseases who are ideal for inclusion in a hiPSC generation project will be from cohorts whose genetic or genomic status has been well characterized (much like one would expect from tissue donors who, although not included in this RFA, suffer from monogenic diseases). Reviewers will be asked to evaluate the rationale for the selection of tissue donors, and will consider this point.

In response to the second question: a key aspect of being a Tissue Collector is having access to the relevant patient populations. For example, if the PI on a RFA 12-02 application is a stem cell researcher, he or she could collaborate with a co-investigator who has access to such patients.

8. RFA 12-02 suggests funding 3 to 10 grants and lists 14 diseases. Does CIRM have a specific number in mind for the number of tissue donors for each disease? A minimum? A maximum? / Do you have a preferred range of sample sizes per disease?

The list of diseases in section II of RFA 12-02 is meant to provide examples of the types of diseases eligible for funding under this RFA. Proposals with a focus on a disease not listed here are also welcome, as long as the disease is genetically complex and prevalent. Although we list 14 diseases, we only expect 3-10 awards. The Grants Working Group reviewers will be tasked with identifying amongst all RFA 12-02 applications those that are most promising with regard to future use of the derived hiPSC lines and their potential impact on disease understanding and mitigation. In addition, the GWG will have to identify a portfolio of applications that is in line with the capacity of the Deriver and the Repository, so the number of awards that will be recommended for funding will partly depend on the number of tissue donors proposed in the top scoring proposals.

CIRM does not have a minimum or maximum number of tissue donors per disease in mind. It will be the responsibility of the applicant to justify the number of tissue donors they propose, a number that they think will be appropriate to address questions regarding that disease; and this will be evaluated by the reviewers.

9. Is there a concern about using EBV-transformed lymphoblastoid cell collections? Will we need to show genomic integrity before hiPSC derivation?

The applicants to RFA 12-02 need to address the potential pitfalls of the cell samples they propose to include in their tissue collection proposal. The Grants Working Group review panel will assess how such pitfalls are likely to affect the utility of the hiPSC resource, and will take that into account when scoring the application.

10. For RFA 12-02, are tissues from autopsy patients eligible for consideration?

Yes, as long as the requirements of the RFA can be met, including collection of viable cells for reprogramming and e.g. availability of appropriate demographic, medical and/or diagnostic information. This would have to be addressed in the proposal.

11. Is there a specific timeframe for the tissue collection?

The RFA 12-02 awards have a two-year project period. You are expected to propose a tissue collection project that can be achieved within that timeframe.

Questions relevant to RFA 12-03

12. You have mentioned in RFA 12-03 that to be eligible for this award, the applicant organization must have secured a location in California at the time of submission of an application. Does this mean we need to have a physical location in California when we apply, or can we wait until we are awarded?

Securing a location in California means to CIRM that there are active negotiations to lease or purchase space as evidenced by a letter of intent or documentation of similar effect; this would be appended to the application in part D, “Supporting Documentation”.

13. According to RFA 12-03, CIRM intends to commit up to $16 million total to support one (1) hiPSC derivation project for up to three (3) years for deriving three hiPSC lines from each of 3000 or more tissue samples (includes control samples). Our calculations suggest that a total of $16 million for the derivation and characterization of 9000 quality lines is incompatible with current costs. Please comment.

CIRM’s intent is to maximize the value of this hiPSC resource and, more generally, the value created with the funds provided by the taxpayers of California. The value of the resource partly depends on the number of hiPSC lines included; the idea is to create a large number of high quality lines for use by researchers in California, and around the country and the world.

After consulting investigators who are deriving hiPSC lines and organizations that are embarking on large-scale hiPSC derivation efforts, CIRM concluded that derivation of hiPSC lines from 3000 tissue donors can be achieved for $16M. We acknowledge that the cost per tissue donor is on the low end. Since hiPSC line characterization is one of the main cost drivers, this means that applicants to RFA 12-03 need to consider whether traditional assays that test hiPSC line quality, such as those for pluripotency and karyotype, can be replaced by more cost effective assays, and whether cost savings can be achieved through optimizing assays for large scale production. We ask that applicants propose derivation programs that balance high quality and cost effectiveness. The applicants will be expected to

propose and justify their choice of assays for evaluating the quality of the lines and they need to create a budget accordingly.

That being said, a prospective applicant who cannot commit to deriving high quality lines from 3000 donors can seek permission to apply with a lower number. To seek that permission, the applicant can request an extraordinary exception, as described in section VI.F on page 6 of RFA 12-03.

14. How many vials per hiPSC lines should the Deriver provide to the Repository? How many cells per vial? At what stage (passage after picking) of hiPSC generation do you want the cells to be cryopreserved?

The intent is for the RFA 12-03 applicants to provide the answers to these questions in their application, as they are the experts. Please do so when describing the hiPSC derivation method (RFA 12-03, section IX.B.9 on page 13). Keep in mind that it will be the Repository's responsibility to expand the hiPSC lines in preparation for distribution or for storage as a reserve.

15. Regarding characterization of hiPSC lines, what are the minimum release criteria to approve the quality of derived hiPSCs? As per RFA12-03, "The Deriver and the Repository shall agree on the full scope of hiPSC line testing required before the transfer of lines to the Repository." Characterization is one of the main cost drivers and would be important to know before we submit a proposal.

CIRM anticipates that the interdependence of activities performed under the 3 RFAs may require individual grantees to make some adjustments. Applicants to RFA 12-03 have the primary responsibility for proposing the hiPSC line characterization assays and minimum release criteria that they believe would ensure the appropriate quality of a pluripotent stem cell line. The reviewers will be asked to assess whether the hiPSC characterization assays proposed by the RFA 12-03 applicants are sufficient and appropriate to establish the quality of the newly derived hiPSC lines.

16. What quality control measures do you really want? Is genomic stability important, or do you expect something like an Oct4 stain only?

In their applications, it is the responsibility of the RFA 12-03 applicants to provide the rationale for the choice of assays used for the characterization of the derived hiPSC lines (RFA 12-03, section IX.B.10 on page 13), and it is the responsibility of the RFA 12-04 applicants to justify the choice of assays for hPSC line characterization prior to release to end-users (RFA 12-04, section IX.B.9d on page 16).

17. People are mosaic and cultures are heterogeneous. Will there be criteria to determine whether the iPSC represent the patient?

Confirming cell identity is an important element of a hiPSC generation effort. It is the responsibility of RFA 12-03 applicants to address cell identity in their hiPSC line characterization assays (using information provided by the Tissue Collectors).

18. Who will be responsible for the quality of the derived hiPSC lines, in particular karyotype, the Deriver or Repository?

Initially the Deriver will be responsible for the characterization of the hiPSC lines, ensuring, amongst other characteristics, they present a normal karyotype or other appropriate measure of genomic integrity. The Repository will be responsible for the quality (including karyotype or related analysis) of the hiPSC when they release them to end users.

19. Will the Genomics Center have any interaction with the hiPSC generation effort – for QC, for example? / Are some of the hiPSC characterization costs going to be covered by the Genomics RFAs and if so, when will we hear about the details of the Genomics RFA? (Note: this refers to RFA 12-06, CIRM Genomics Awards, to be released in August 2012)

The Genomics Center will not be fulfilling a QC role during the hiPSC derivation effort by the Deriver. It is the Deriver's responsibility to ensure that the hiPSC lines are of the appropriate quality; the RFA 12-03 applicants will elaborate on the characterization methods they propose to use to evaluate the quality of the newly derived lines (RFA 12-03, section IX.B.10 on page 13). The Repository will have the responsibility of maintaining the quality of those lines (see e.g. RFA 12-04, section IX.B.9d on page 16).

The Genomics RFA is planned for release in August; make sure that you are signed up on our website to receive notifications of RFA releases.

20. What percentage of primary cells will not be skin or blood derived?

This is not yet known, and will depend on the needs of the Tissue Collectors selected for funding. In terms of costs for the Deriver to prepare the tissue samples for derivation and also for shipment to the Repository, the RFA 12-03 applicants should develop a budget based on their preferred tissue type, and assume a certain percentage (e.g. 80%) of samples to be collected from that tissue type. The cost calculations for the remainder of tissue samples should be based on the proposed alternate tissue type.

21. If a skin biopsy is collected, who is responsible for generating the fibroblasts?

It is stated in RFA 12-03 (section III, Primary Source Cells, page 3) that the "Deriver will expand, if appropriate, and cryopreserve cells from all original tissue samples (primary source cells)." In the application (RFA 12-03, section IX.B.8 on page 13), the applicant is asked to

"describe the protocol used for expansion, if indicated, cryopreservation and shipment of primary source cells for long-term storage at the Repository."

CIRM's intent is that for skin, the Tissue Collector ships the biopsy material to the Deriver, who will prepare the fibroblast cultures from the biopsy material.

22. Does DNA rearrangement in blood cells matter?

The applicants who propose tissue collection protocols using blood need to address this point.

Questions relevant to RFA 12-04

23. For the CIRM hPSC Repository Award, if an organization has facilities in both California and in another state, can the hiPSC lines be prepared and cryopreserved in the other state and stored and distributed from California?

The short answer is no. Although an RFA 12-04 applicant organization does not have to be located in California at the application deadline, CIRM expects the Repository, once funded, to be located in California; as stated under "Institutional Eligibility", the Repository has to be present and operated in California. Importantly, only very limited funds can be used for out-of-California activities, as stated in the budget guidelines on page 14, section IX.B.5 under Consultants/Subcontracts.

24. Who will be responsible for the quality of the derived hiPSC lines, in particular karyotype, the Deriver or Repository?

Initially the Deriver will be responsible for the characterization of the hiPSC lines, ensuring, amongst other characteristics, they present a normal karyotype or other appropriate measure of genomic integrity. The Repository will be responsible for the quality (including karyotype or related analysis) of the hiPSC when they release them to end users.

25. Will the primary source cell lines be redistributed to any investigator who requests them?

CIRM's main purpose for banking of primary source cells is for re-derivation of hiPSC lines should the need arise due to problems with the original 3 lines. As this should be a rare request, we suggest that primary source cells do not need to be readied for distribution until a request is made.

26. Will the 2 hiPSC lines per tissue donor stored as a reserve be distributed, as they may not have exactly the same differentiation potential as the clone used for primary distribution?

All 3 hiPSC lines derived from each tissue donor will have met minimum release criteria following derivation. The 2 hiPSC lines stored as a reserve should be distributed if requested although neither the Deriver nor the Repository can guarantee that they will behave exactly like the primary line.

27. How many additional cell lines, generated outside this hiPSC Initiative, are expected to be banked?

CIRM sees a need for roughly 100-200 human pluripotent stem cell lines (hiPSC and hESC) generated by California investigators to be banked by the Repository. As requested in the application (RFA 12-04, section IX.B.8b), RFA 12-04 applicants should develop minimum acceptance criteria for inclusion of an hPSC line in the Repository, ensuring that only lines of appropriate quality are included.

General Questions relevant to the hiPSC Initiative

28. How will the reviewers balance a 12-03 application that plans to provide for example, 2 vials per line and a banking application that requires, for example, 6-10 vials to start the bank? Will there be a chance to coordinate these activities to minimize costs?

Yes, after approval of award funding by CIRM's governing board, CIRM will convene a meeting of all hiPSC Initiative Awardees to facilitate coordination of activities (See section III, last item, in all 3 hiPSC Initiative RFAs). CIRM will also negotiate with Awardees specific activities and deliverables prior to Notice of Grant Award with the goal in mind to promote the successful execution of the entire hiPSC Initiative.

29. Is there a limit to the number of pages of supporting documents that can be submitted under Part D, such as dozens of pages of Protocols and SOPs? Also, can we submit scientific data under Part D?

There is no official limit, but in order to avoid overwhelming reviewers with material, CIRM suggests you provide just a few representative SOPs in Part D.

For RFAs 12-03 and 12-04, we ask that you provide a list of or a link to SOPs in either the Part B application (see RFA 12-03, section IX.B.11, page 13 and RFA 12-04, section IX.B.10, page 17) or in Part D.

Submission of scientific data under Part D is not permitted. Please include such data in the relevant portions of the Part B application, where we ask you to provide or to cite evidence that validates the choice of assay, e.g., and where you think it is appropriate.

30. RFA 12-02 describes both facilities and indirect costs. What is the difference? And, are such costs part of, or in addition to, the $4 million total costs set aside for these awards? (Although directed at RFA 12-02, this question and answer applies to all 3 hiPSC Initiative RFAs)

Facilities Costs cover general operating costs of the Grantee's facilities attributable to housing all elements of the CIRM-funded Project or Activity. Indirect costs are administrative costs incurred for common or joint objectives, which cannot be readily and specifically identified with a particular project. See section IX.B.5. for a further description of "Facilities Cost" and "Indirect Costs". Both Facilities and Indirect costs are part of the $4M total cost set aside for RFA12-02 awards.

31. Just to be clear, the $16 million for the Deriver includes institutional indirect cost? (Although directed at RFA 12-03, this question and answer applies to all 3 hiPSC Initiative RFAs, each with a different $ amount)

Yes. That is the total award.

32. Who is responsible for pathogen testing (e.g. HIV, HBV, etc.) of the primary tissue sample? The collector or the deriver?

Because the derived cells are not intended for human transplantation, there is no requirement to test the primary tissue samples for the presence of human pathogens. From tissue collection through hiPSC generation and banking, to third party use, the cells shall be handled according to standard biosafety guidelines and should be treated as though they are contaminated with infectious agents.

33. Will all MTAs need to go through an approval loop through CIRM?

CIRM's approval of template agreements, and any material deviations with respect to same is required and CIRM reserves the right to require prior approval of individual MTAs. Refer to Appendix B to each RFA.

34. Can an individual apply to more than one RFA?

Yes, an individual can apply as PI or PD to more than one hiPSC Initiative RFA, but an individual can only apply once to a given RFA. Of note, we do have a percent effort requirement, which may limit the number of RFAs some investigators can apply to, depending on their other commitments.

35. For RFA 12-02/12-03, if more than 3000 samples are contributed, what are the criteria for the tissue expansion and iPS cell derivation?

Beyond identifying the best proposals, one goal of the Grants Working Group review will be to harmonize the capacity of the Deriver and the Repository with that of the RFA 12-02 applications that will be recommended for funding (CIRM's governing board, the ICOC, will make the final funding decisions). Each RFA 12-02 applicant will propose and justify a certain tissue donor number to be included in their project, and the reviewers will have to use those numbers as they arrive at a portfolio of diseases to be recommended for inclusion in this Initiative. CIRM expects that when the RFA 12-02 awards are made, the total number of tissue donor samples will match the number in the award under RFA 12-03.

36. Are there more details for the shipping and distribution of the material?

No details are yet available for the shipping and distribution of cells, as applicants will propose these details. The Deriver is expected to provide the tissue shipping protocols to the Tissue Collectors (RFA 12-03, section IX.B.8) with certain exceptions: 1) if skin or blood cannot be collected from a given patient population, the RFA 12-02 applicant will propose a tissue collection and shipping protocol; 2) in the case that the Tissue Collector includes existing banked cells, they will be responsible for arranging shipping from the existing Repository.

RFA 12-04 applicants are asked to propose shipping methods for incoming primary source cells, pluripotent stem cell lines, and for distribution of cells to third parties (RFA 12-04, section IX.B.9b).

37. Will the CIRM hiPSC Initiative only fund big centers? Is it a waste of time for innovative young investigators to apply for this opportunity?

This opportunity comprises three RFAs.

For RFA 12-02, the tissue collection proposals are likely to come from individual clinicians or investigators or small teams who have access to specific patient populations. Depending on the targeted disease, a proposal could target a relatively small cohort of tissue donors. It is the responsibility of the applicant to justify the size of the tissue donor cohort. So this particular funding opportunity would

be attractive to individual investigators.

By contrast, for RFAs 12-03 and 12-04, the capacity to derive or bank the hiPSC lines and associated primary source cell samples needs to be very large. The successful execution of these projects will depend on experience with large-scale operations working under standard operating procedures. It seems that these 2 RFAs may be of less interest to individual investigators.

38. Why does RFA 12-02 target polygenic diseases?

Monogenic diseases are being widely pursued for hiPSC modeling by the scientific community. The goal of this Initiative is to generate a unique resource that will be useful for research for the next decade. Furthermore, monogenic diseases tend to be rare; by targeting polygenic diseases we can also focus on prevalent diseases, thereby increasing the potential impact of this resource on disease understanding and mitigation. We do believe that polygenic diseases are amenable for research use with hiPSC technology and there is evidence that polygenic diseases can be modeled in hiPSC lines, such as schizophrenia.

39. Because of the focus on polygenic diseases in RFA 12-02, there are no hESC lines that represent these diseases. Will there be a separate opportunity for hESC collections?

CIRM is not planning on releasing an RFA that specifically focuses on the generation of new hESC lines, but hESC derivations are appropriate under other CIRM RFAs. The Repository will be charged with not only banking hiPSC lines derived under RFAs12-02 and 12-03, but also with banking pluripotent stem cell lines that have been derived by the stem cell community in California; this would include hESC lines (see footnote 1 in all RFAs).

40. Will the same group of reviewers be reviewing 12-03 and 12-04 (hiPSC generation and banking)?

Yes. We will have as part of the Grants Working Group review team experts with knowledge relevant to the 12-03 review criteria and experts with knowledge relevant to the 12-04 review criteria.

41. Drug toxicity is the 4th leading cause of death in the US. Ethnically or genomically diverse iPSCs could be used to test drugs for toxicity early in the pipeline. Does CIRM have an interest in using iPSC for toxicity testing during drug development?

Yes, CIRM has an interest in the use of hiPSC technology for toxicity testing. We conducted a toxicology workshop in 2008 and the report from that workshop is posted on our website here. CIRM also funds several grants in this area.

In the context of RFA 12-02, each application will need to be focused on a specific disease. However, the resulting hiPSC lines can be chosen by the end user based on ethnicity or other genomic diversity for toxicity studies.

42. Will there be opportunities for interaction with the grantees by researchers who regularly make their own iPSCs? A lot of researchers have valuable tissue collections already established. Will they be able to make use of the infrastructure?

CIRM very much welcomes inclusion of existing patient cohorts or existing tissue collections that are well characterized in RFA 12-02 applications. It is further expected that the Repository will bank lines already generated by California investigators.

Once CIRM's governing board makes its funding decisions for the hiPSC Initiative, the scientific community will be aware of who has received an award; we encourage discussion and interaction amongst our grantees and between our grantees and other researchers.
